Remarks/Arguments

Claims 58-63 are presently in the case.

Claim Rejection - 35 U.S.C. § 101

Claims 58-63 stand rejected under 35 U.S.C. 101 allegedly because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Applicants disagree with the Examiner for the following reasons.

Utility Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility." (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P, 2107 II (B) (1) gives the following instruction to patent examiners: "If the (A)pplicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be

considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the Applicant's assertions." (M.P.E.P. 2107 II (B) (1) (ii)). Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

To overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.** Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Further, the legal standard with respect to *in vitro* or animal model data providing pharmacological activity has been commented on in *Cross v. Iizuka*, 753 F.2nd 1040, 1051, 224 USPQ 739, 747-48 (Fed. Cir. 1985):

> "We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vitro* utility."

Furthermore, M.P.E.P. 2107.03 (III) states that:

> "If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process."

Thus, the legal standard accepts that *in vitro* or animal model data is acceptable utility as long as the data is "reasonably correlated" to the pharmacological utility described.

Arguments

(1) First, Applicants rely on the identification of the PRO701 protein as a neuroligin based on homology data. The Office Action indicates that the invention is not supported by either a specific and substantial or credible asserted utility. However, the Office Action does not provide any reasons why this utility is not specific, substantial or credible. Absent any such reasons applicants maintain that the utility is specific, substantial and credible and request withdrawal of this rejection.

This utility was first disclosed in U.S. Serial 60/080,328 filed April 1, 1998. At page 21, lines 4 - 7 of U.S. Serial 60/080328, Applicants indicate that the PRO701 polypeptide of the invention possesses the biological activity related to that of the neuroligin family. On page 1, lines 9 - 25, Applicants state the following:

> "Beta neurexins and neuroligins are plasma membrane proteins that are displayed on the neuronal surface. Neuroligin 1 is enriched in synaptic plasma membranes and act as a splice site-specific ligand for beta neurexins as described in Ichtenko et al., Cell 81(3):435-443 (1995). The extracellular sequence of neuroligin 1 is composed of a catalytically inactive esterase domain homologous to acetylcholinesterase. Neuroligin 2 and 3 are similar in structure and sequence to neuroligin 1. All neuroligins contain an N-terminal hydrophobic sequence with the characteristics of a cleaved signal peptide followed by a large esterase homology domain, a highly conserved single transmembrane region and a short cytoplasmic domain. The three neuroligins are alternatively spliced at the same position and are expressed at high levels only in the brain. Tight binding of the three neuroligins to beta neurexins is observed only for beta neurexins lacking an insert in splice site 4. Thus, neuroligins constitute a multigene family of brain-specific proteins with distinct isoforms that may have overlapping functions in mediating recognition processes between neurons, see Ichtchenko et al., J. Biol. Chem. 271(5): 26776-2682 (1996). Moreover, neurexins and neuroligins have been reported as functioning as adhesion molecules in a Ca^{2+} dependent reaction that is regulated by alternative splicing

of beta neurexins, i.e. see Nguyen and Sudhof J. Biol. Chem. 272(41):26032-26039 (1997)."

There are a number of papers which were published prior to applicants priority document which set forth the function of neuroligins in general. For example, Ichtchenko et al., Cell 81(3):435-443 (1995) (previously provided) discusses neuroligin 1. It indicates that subcellular fractionation of brain demonstrated that neuroligin 1 is enriched in synaptosomes similar to the post synaptic density protein PSD95 (page 438, col. 2). Ichtchenko also teaches that neuroligin 1 copurifies with PSD95 on synaptic plasma membranes. Ichtechenko suggests that the surface expression of neuroligin 1 and β-neurexins on neurons leads to tight interactions between these neurons. Ichtchenko teaches that neuroligin 1's interaction with neurexin contributes to the organization of the synapse, thereby increasing the specificity of the interactions or specifying a defined sequence of interactions. (page 441, col. 2)

Ichtchenko et al., J. Biol. Chem. 271(5): 26776-2682 (1996) (previously provided) teaches two neuroligins, neuroligins 2 and 3, which are similar in structure and sequence to neuroligin 1. All three neuroligins bind to β-neurexins. Ichtechenko indicates that neuroligins mediate cell-cell interactions between neurons.

Nguyen and Sudhof, J. Biol. Chem. 272(41):26032-26039 (1997) (previously provided) discusses that the binding properties of Neuroligin 1 and Neurexin 1 reveal that these molecules function as heterophilic cell adhesion molecules for mediating cell recognition between neurons. Nguyen and Sudhof also indicate that the esterase-like domain is involved in binding the neurexins. Since the binding properties of neuroligins 2 and 3 are similar to neuroligin 1, they state that the binding of neurexins and neuroligins forms the nucleus for an intercellular junction.

Finally, Irie et al., Science 277:1511-1515 (1997) (copy enclosed) also indicates that the extracellular domain of neuroligins 1, 2 and 3 tightly bind to the extracellular domain of neurexins. The cytoplasmic domains of all three neuroligins (1,2,and 3) interact with the amino terminus of PSD-95. They indicate that neuroligins 1, 2 and 3 and neurexins form an intercellular junction between nerve cells. The PSD-95 attach to the cytoplasmic tails of the neuroligins 1, 2 and 3 and recruit NMDA2 receptors and K+ channels to the neuroligin side of the junction.

Clearly it was known in the art at the time Applicants filed their provisional application that neuroligins were involved in mediating the cell-cell recognition between nerve cells, likely at the synapses. Applicants identified a novel neuroligin with these properties.

After the filing of the provisional patent application, Bolliger et al., *Biochem J.* (2001) 368 581-588 (previously provided) confirmed the structure and function of neuroligin 4 as set forth by Applicants in the provisional application. Bolliger et al., identified that neuroligin 4 binds to the PDZ domains of PSD-95, which is a art recognized characteristic of neuroligins. Another paper, Jamain et al., *Nature Genetics*, vol. 34, 27- 29 (May 2003) (previously provided) which indicates that mutations of neuroligin 4 are associated with autism. Accordingly, Applicants' discovery and characterization of PRO701 (now named neuroligin 4 in the literature) was subsequently independently confirmed by other researchers.

Based on Applicants disclosure in Serial No. 60/080,328, the knowledge in the art at the time of filing, Applicants maintain that the claims are fully enabled. Applicants correctly identified the PRO701 polypeptide as a neuroligin and hence the inherent utility of the PRO701 polypeptide as mediating the cell-cell recognition between nerve cells through a heterophilic junction. Later published works by others have simply recognized and confirmed the sequence and inherent utility of the PRO701 polypeptide previously described by Applicants in their priority document.

(2) Second, Applicants rely on the " Rat DRG neuronal survival inhibition assay ASSAY #58" for patentable utility for the PRO701 gene and the PRO701 protein and antibodies thereof. This assay first disclosed in PCT/US00/04341 (18 February 2000) and in U.S.S.N. 09/918,585 (30 July 2001) also establishes patentable utility.

The Examiner states that the ability of the PRO701 protein to inhibit the survival of E14 rat embryo dorsal root ganglia is not a credible use because the cells cultured in this assay are not representative of adult neural cells and tumor cells. It is allegedly well known in the art that sensory neurons undergo programmed cell death during early embryonic development. (Oppenheim *Annu. Rev. Neurosci* (1991) Vol. 14, pp 453-501) The art allegedly also teaches that factors that cause neonatal cell death, such as peripheral nerve injury, growth factor withdrawal, ionizing radiation, capsaicin do not have the same effect on adult neural cells. Adult

neural cells are allegedly more resistant to these factors (Lewis et al., *J. Neuroscience*, Oct. 1999, Vol. 19(20) pp8945-8953). This is allegedly further exemplified by Memberg et al. who teaches that the survival of neural cells depends on specific factors and that the factor dependence changes with the age of the neural cells. There is allegedly no art-known nexus between the cell growth of neurons in this assay and the predictable treatment of neuropathies and undesirable neural cell proliferation.

First, Applicants note that the DRG neuronal survival assay is a well recognized and well used assay for measuring compounds which affect the growth of neural cells. The Examiner agrees that the rat DRG neuronal assay has been used in the art to study the effects of various factors on neural development. Applicants note that in vitro sensory ganglia survival and outgrowth assays were used by Levi-Montalcini to identify Nerve Growth Factor. (See excerpt from *Principle of Neural Science,* 4th Ed., Kandel ed. (1991) p1056, previously provided). Secondly Applicants note that both Lewis et al. and Memberg use the DRG survival assay for their analysis. Memberg indicates that proliferation in culture of DRG neuroblasts is consistent with *in vivo* data (page 330, column 1). Clearly this assay is art recognized as being useful to identify compounds with various effects on neural development.

Secondly, in Memberg, the comparison was between E12 rat cells and E14.5 rat cells, not between adult and E14.5 rat cells. Memburg indicates that NGF and NT3 act as neurotrophins for E14.5 DRG cells. Memburg does not test whether the neurotrophins which stimulate survival of E14.5 cells are different from those that stimulate survival of adult rat cells. Applicants used E14 rat embryo cells in their assay. This is essentially the same age neurons as Memberg. Memberg does not teach that the use of these neurons is inappropriate.

The Examiner cites Lewis et al. as evidence that adult neural cells are more resistant to peripheral nerve injury. Lewis measured the regulation of HSP27 in DRG of rats by counting the total numbers of HSP27 immunoreactive neurons at postnatal days 2, 7 and 21. Lewis does not measure the regulation of HSP27 in embryonic DRG cells. One of the assays Lewis uses in making his final determination regarding the effect of HSP27 is the DRG survival assay. Lewis determines that the expression of HSP27 confers a survival advantage to neonatal sensory neurons after injury or NGF deprivation. Clearly Lewis, as do others in the field, agree that the DRG neuronal survival assay is a recognized method of assaying for neurotrophic factors.

As set forth in MPEP 2107 II (B) (1), if the applicant has asserted that the claimed invention is useful for any particular practical purpose and the assertion would be considered credible by a person of ordinary skill in the art, a rejection based on lack of utility should not be imposed. The logic underlying the asserted utility in the present case is not inconsistent with the general knowledge in the art, and would be considered credible by a person skilled in the art.

The remaining issue is whether there is sufficient nexus between the *in vitro* data disclosed in the specification and the results a skilled artisan would expect in the treatment of neuropathies. "Nexus" requires a factually and legally sufficient connection between the objective evidence provided and the claimed invention, so that the evidence is of probative value in the determination of the issue that it is purported to support. There are peer-reviewed papers in the literature where the authors have used the DRG survival assay to identify neurotrophins and compounds which inhibit neuronal growth. The Examiner admits that the assay has been used to study the effects of various factors on neural development. Finally, this assay or one similar to it was used in the identification of Nerve Growth Factor which is recognized as being a neurotrophin. Positive results with a drug candidate in a recognized *in vitro* assay have long been recognized by the Patent Office and competent courts as sufficient to support utility for claims covering compounds.

Thus, Applicants believe that they have established patentable utility for PRO701 and its antibodies as instantly claimed and this rejection should be withdrawn.

Claim Rejections - 35 U.S.C. § 112, first paragraph

Claims 59-66 and 68-85 stand rejected under 35 U.S.C. 112, first paragraph. Since the claimed invention is allegedly not supported by either a specific and substantial or credible asserted utility or a well established utility , one skilled in the art would allegedly not know how to use the claimed invention.

Applicants maintain for the reasons set forth in the section of utility that the invention is supported by either a specific and substantial or credible asserted utility or a well established utility. and accordingly, one skilled in the art would know how to use the invention. Withdrawal of this rejection is respectfully requested.

Priority

Applicants note that the subject matter defined in claims 58-62 has been accorded an effective filing date of October 16, 2001 because the instant specification disclosure allegedly fails to meet the requirements of 35 U.S.C. §§ 101 and 112, first paragraph. Accordingly, the claim for priority to any parent application has been denied.

Applicants maintain that the subject matter defined in claims 58-62 is entitled to the priority date of April 1, 1998, the filing date of Provisional Patent Application Serial No. 60/080328. At page 21, lines 4 - 7 of U.S.S.N. 60/080328, Applicants indicate that the PRO701 polypeptide of the invention possesses the biological activity related to that of the neuroligin family. On page 1, lines 9 - 25, Applicants indicate that neuroligins constitute a multi-gene family of brain-specific proteins with distinct isoforms that have overlapping functions in mediating recognition processes between neurons. Moreover, neurexins and neuroligins have been reported as functioning as adhesion molecules in a Ca^{2+} dependent reaction that is regulated by alternative splicing of beta neurexins. (See also the discussion under utility)

In Serial No. 60/080328, Applicants referenced Ichtchenko et al., *J. Biol. Chem.* 271(5):2676-2682 (1996) and Nguyen and Sudhof, *J. Biol. Chem.* 272(41) 26032-26039 (1997) as references which describe the function of other related neuroligins.

Based on Applicants disclosure in Serial No. 60/080328, Applicants maintain that they are entitled to priority to the filing date of Serial No. 60/080328, i.e. April 1, 1998. Applicants correctly identified the polypeptide and the utility of the PRO 701 polypeptide. Later published works by others, Bolliger and Jamain (previously discussed) have confirmed the sequence and utility of the PRO701 polypeptide described by Applicants in their priority document.

Applicants maintain that the subject matter defined in claims 58-62 is also entitled to the priority date of February 18, 2000, International Patent Application Serial No. PCT/US00/04341. At pages 369-370, Example 140 of PCT Application No. PCT/US00/04341, Applicants indicate that the PRO701 polypeptide of the invention possesses the biological activity related to the inhibition of survival of neural cells in culture. Based on Applicants disclosure in PCT Application No. PCT/US00/04341, Applicants maintain that they are entitled to priority to the filing date of February 18, 2000 for these claims.

35 U.S.C. § 102

Claims 58-62 stand rejected under 35 U.S.C. 102(b) as being anticipated by Ichtchenko et al. (1995). Specifically, Ichtchenko et al. teaches an antibody that binds to a neuroligin protein. Applicants discloses that the protein to which the claimed invention binds has homology to neuroligin proteins. Accordingly, the antibody of Ichtchenko et al. would allegedly bind to the same protein in which the claimed invention binds.

Applicant specifically traverses this rejection for the following reasons.

First of all, Claim 58 , and, consequently, those claims dependent from the Claim 58, recite "an antibody that binds specifically to the polypeptide of SEQ ID NO:375." (Emphasis added). Applicants respectfully submit that the term "specific binding" recited in Claim 58 refers to an antibody that binds to a particular antigen without binding to another antigen. Therefore, Claim 58 and the claims dependent from Claim 58, carrying its recitations, clearly refer to an antibody that is able to bind to the PRO701 polypeptide *without* cross reacting with another antigen, including the sequence disclosed in Ichtchenko *et al.* In view of this, the Examiner errs in assuming that the antibodies claimed in the present application would bind the polypeptide of Ichtchenko. While the amino acid sequence of neuroligin 1 taught by Ichtchenko et al. has some similarity to the PRO701 sequence, there are many different amino acid residues throughout the length of the sequences. As a result of the requirement of specific binding, the claims pending in this application do not encompass antibodies that bind to the polypeptide of Ichtchenko *et al.* As the Examiner is well aware, an antibody generally recognizes only a small region on the surface of a large molecule and the structure recognized by an antibody is called an epitope. The structures generally recognized by the antibody are located on the surface of the protein and such sites are likely to be composed of amino acids from different parts of the polypeptide chain that have been brought together by protein folding. Epitopes of this kind are known as conformational or discontinuous epitopes because the structure recognized is composed of segments of the protein that are discontinuous in the amino acid sequence of the antigen but are brought together in the three-dimensional structure. Most antibodies raised against intact, fully folded proteins recognize discontinuous epitopes.

Second, the binding sites for the claimed antibodies cannot be simply predicted based on the linear sequence homology between the amino acid sequence of present invention and that of Ichtchenko *et al*. In view of the fact that most antibodies recognize discontinuous epitopes and not linear epitopes, it is even less likely that an antibody will recognize and bind to linear fragments of a protein sequence.

In a related case, U.S. Serial No. 09/978,802, the Patent Office cited Irie et al., as evidence by a Sequence Alignment. Applicants note that the EMBL AB033086 and BAA86574 references listed in the Sequence alignment were provided in the BLAST results provided in an earlier Information Disclosure Statement. Applicants enclose another Information Disclosure Statement which provides Irie et al. and additional information regarding the BLAST results previously provided. As can be see from the enclosed documents, AB033086 was publicly available on Nov. 11, 1999 and BAA86574 was submitted on October 4, 1999.

Applicants had previously indicated that they claimed priority to PCT Patent Application No. PCT/US99/05028, Wood et al., filed 3 March 1999 in the original declaration filed . Under the section entitled Priority, Applicants have also claimed priority back to U.S. Serial No. 60/080328 filed April 1, 1998 on the basis that this application discloses the sequence and utility for PRO701.

Applicants have also asserted priority to the date of February 18, 2000, International Patent Application Serial No. PCT/US00/04341 based on Example 140, inhibition of survival of neural cells. This date is within 1 year of the October 4, 1999 date of BAA85674. Accordingly, this reference is at best a reference under 35 U.S.C. 102(a) and Applicants are entitled to provide a Declaration under 37 C.F.R. 1.131 antedating the reference.

Applicants submit that U.S. Serial No. 60/080328 filed April 1, 1998 simply needs to provide a disclosure commensurate in scope with the disclosure in the cited art to antedate the reference. Applicants enclose herewith a Declaration under 37 C.F.R. 1.131 referencing U.S. Serial No. 60/080328.

In *In re* Stempel (1957) 113 USPQ 77, the patent applicant (Stempel) had claims directed to both (i) a particular genus of chemical compounds (the "generic" claim) and (ii) a single species of chemical compound that was encompassed within that genus (the "species" claim). In support of a rejection under 35 U.S.C. § 102, the examiner cited against the Stempel application

a prior art reference that disclosed the exact chemical compound recited in Stempel's "species" claim. In response to the rejection, Stempel filed a declaration under 37 C.F.R. §. 1.131 demonstrating that he had made that specific chemical compound prior to the effective date of the cited prior art reference. The CCPA found Stempel's 131 declaration effective for swearing behind the cited reference for purposes of both the "species" claim and the "genus" claim. Specifically, the CCPA stated in support of its decision:

"We are convinced that under the law all the applicant can be required to show [in a declaration under 37 C.F.R. §. § 1.131] is priority with respect to **so much of the claimed invention as the reference happens to show**. When he has done this he has disposed of the reference." (Id. at 81; emphasis supplied).

Secondly, the Examiner is respectfully directed to *In re* Moore, 170 USPQ 260 (CCPA 1971), where the Stempel rule was extended to cases where a reference disclosed the claimed compound but failed to disclose a sufficient utility for it. More specifically, the patent applicant (Moore) claimed a specific chemical compound called PFDC. In support of a rejection of the claim under 35 U.S.C. § 102, the examiner cited a reference which disclosed the claimed PFDC compound, but did not disclose a utility for that compound. Applicant Moore filed a declaration under 37 C.F.R. § 1.131 demonstrating that he had made the PFDC compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. On appeal, the CCPA indicated that the 131 declaration filed by Moore was sufficient to remove the cited reference. The CCPA relied on the established "Stempel Doctrine" to support its decision, stating:

An applicant need **not** be required to show [in a declaration under 37 C.F.R. § 1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference....the determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes. (Id. at 267, emphasis supplied).

Thus, *In re* Moore confirms the Stempel rule holding that in order to effectively remove a cited reference with a declaration under 37 C.F.R. § 1.131, an applicant need only show that portion of his or her claimed invention that appears in the cited reference.

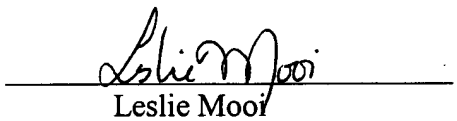
Applicants have claimed priority to U.S. Serial No. 60/080328, filed April 1, 1998. Applicants maintain that they should be entitled to priority to this application to remove prior art references with similar disclosures consistent with the teachings of *In re* Stempel and *In re* Moore.

All claims pending in this application are believed to be in prima facie condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including additional fees for extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2630P1C21. Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: April 11, 2005



Leslie Mooi
Reg. No. 37,047

HELLER EHRMAN WHITE & McAULIFFE LLP
Customer No. 09157/35489
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

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